Pathophysiology and treatment

This is the second part of a two-part history of psoriasis. In part one, published in Issue 53, I discussed the evolution in our understanding of the disease, based on the descriptive appearance of psoriatic skin lesions and how these were eventually recognised as representing a disease in its own right.

In part two, I will discuss how our understanding of the underlying disease processes (pathophysiology) has evolved and provide a brief history of the various approaches to treatment over the past 200 years. It is a remarkable story of serendipity and great science.

Pathophysiology

The essential finding in psoriasis is that cells in the epidermis (the outer layer of the skin) multiply up to ten times faster than normal. This process is called epidermal hyperplasia and it results in the thickening, crusting and scaling of the skin so characteristic of psoriasis.

The process of epidermal hyperplasia in psoriatic patients was first observed by E.J. Van Scott in 1963. Three years later, Van Scott and Weinstein noted that skin cells in psoriatic patients rose to the surface in only two days, in contrast to their 12-day transit through normal epidermis. This rapid turnover of epidermal cells was soon shown to be the result of a cascade of autoimmune reactions – meaning that part of the body's immune system becomes overactive and attacks normal tissues. This then results in the release of special inflammatory molecules called cytokines, and the resulting inflammation leads to the characteristic features of psoriasis – reddened, thickened, dry and scaly skin.

Today, we recognise psoriasis to be the result of a complex interaction between immunological, genetic, cellular, and environmental factors. Moreover, numerous studies have unequivocally shown that psoriasis is a systemic inflammatory disease which may have adverse consequences in other organs – including in the heart, liver, kidneys, intestines, muscles and tendons.

The good news is that this rapid development in our scientific understanding of the fundamental mechanisms involved has led to remarkable advances in treatment – to which I now turn.

From arsenic to biologics – a 200-year history of treatments

In 1726, Turner described treating psoriasis with an ointment containing ammoniated mercury or with a broth of boiled vipers. It isn't clear whether any improvement (assuming there was any) was due to the mercury or the boiled viper casserole but (as we will see), in the 19th century both mercury and arsenic were recommended as treatments. These early forms of treatment tended to be internal rather than topical because it was believed that applying medications to skin lesions could drive them inwards and thus affect the internal organs.

19th century – arsenic and ammoniated mercury

Thomas Girdlestone was an English physician and writer who, in 1806, is said to have been the first to advocate the use of arsenical compounds in the treatment of psoriasis – though arsenical compounds had, in fact, been used to treat skin diseases since at least Roman times.

Girdlestone prescribed a solution of 1% potassium arsenite – Fowler's solution – usually given as six drops, three times daily. Other physicians began to recommend the same treatment, which did appear to have some benefit, though mainly in the guttate form of psoriasis. Then, in 1869, Lipp introduced subcutaneous injections of arsenous acid for patients with psoriasis or eczema.

The problem, of course, is that arsenic is one of the most toxic metals derived from the natural environment. It accumulates in the internal organs, causing a range of terrible side effects (which is why it has always been so attractive to the poisoner). It is also a potent carcinogen (cancer-causing agent). Despite this, arsenic preparations remained in use until the middle of the 20th century, when corticosteroids were first introduced.

Mercury was used for centuries in the treatment of skin disease and – notably – syphilis. The great Austrian composer Franz Schubert died from syphilis in 1828 at just 31 years of age. In those days the patient (or perhaps victim) was placed in a sealed room and covered with mercury. They were forbidden to change either their clothing or bed sheets. Patients would complain of abdominal pains, difficulty swallowing, headaches, diarrhoea, and muscle weakness. The doctors explained that these were simply temporary side effects of an effective treatment, but in fact these are all symptoms of chronic mercury poisoning.

Schubert died in Vienna, at the apartment of his brother Ferdinand. He had been unable to eat properly for days and had also become confused. The official cause of death was given as typhus, but this seems unlikely. The more likely explanation is that, although he did have syphilis, it was the treatment rather than the disease that killed him.

For psoriasis, on the other hand, mercury was most often applied as an ointment and remained in use until quite recently. In fact, a letter in the British Medical Journal of 1956 says "mercury ointments are still widely used in the treatment of psoriasis...". As with arsenic, it accumulates in the body and – as we have seen - has potentially serious toxic effects. Interestingly, however, the signatories of the BMJ letter (Inman, Gordon and Trinder), say, "Toxicity due to mercury absorption in the treatment of psoriasis must be rare, and has not been recognised in this clinic". So perhaps in the ointment form, mercury was somewhat less dangerous.

1900-1950 – dithranol (anthralin) and tar

In 1876, Squire inadvertently found dithranol to be an effective treatment for psoriasis. He had prescribed Goa powder, which was until then known only to be effective in ringworm, and the patient's psoriasis improved.

Goa powder is the dried, powdered rubbery sap (latex) from a Brazilian tree called Andira araroba. It turns out that the active ingredient of Goa powder is chrysarobin, also known as 2-methyl dithranol. A synthetic form of dithranol was first produced in 1916 and was then introduced as a therapeutic agent for skin disease by Galewsky.

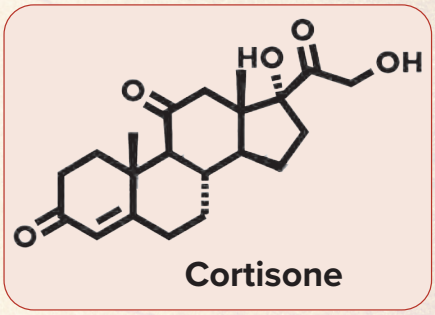
Dithranol was first used in Germany, and later in

Britain, but it has never been popular with American dermatologists, probably due to the side effects of staining and irritation of the skin.

The next big advance in psoriasis treatment was coal tar. Hippocrates and other ancient physicians treated skin conditions with pine tar and other types of tar. Coal tar became available when coal gas production developed in the late 19th century and William Goeckerman – an American dermatologist - found it to be very effective in the treatment of psoriasis. It had an anti-inflammatory action but, unfortunately, it also had an unpleasant odour and some potential for skin irritation. Recognising that summer sun was also helpful in psoriasis, in 1925 Goeckerman showed that a combination of coal tar and UV light was especially effective. Then, in 1953, John Ingram, an English dermatologist, added dithranol paste to UV light and coal tar – known as the Ingram Regimen. Ingram went on to establish the first day-care facility for psoriasis and this general approach remained a cornerstone of psoriasis treatment for decades.

1950s – corticosteroids

In 1950, Hench, Kendall, and Reichstein received the Nobel Prize for the development of cortisone, which heralded the corticosteroid era and a revolution in the treatment of many diseases. Just two years later, cortisone was used as a topical preparation in various skin diseases, though had a limited effect in psoriasis.



Cortisone

However, a variety of synthetic corticosteroids soon followed, which proved to be extremely efficacious in the treatment of psoriasis. There are, however, unwanted effects, including thinning of the skin, and these limit their long-term use.

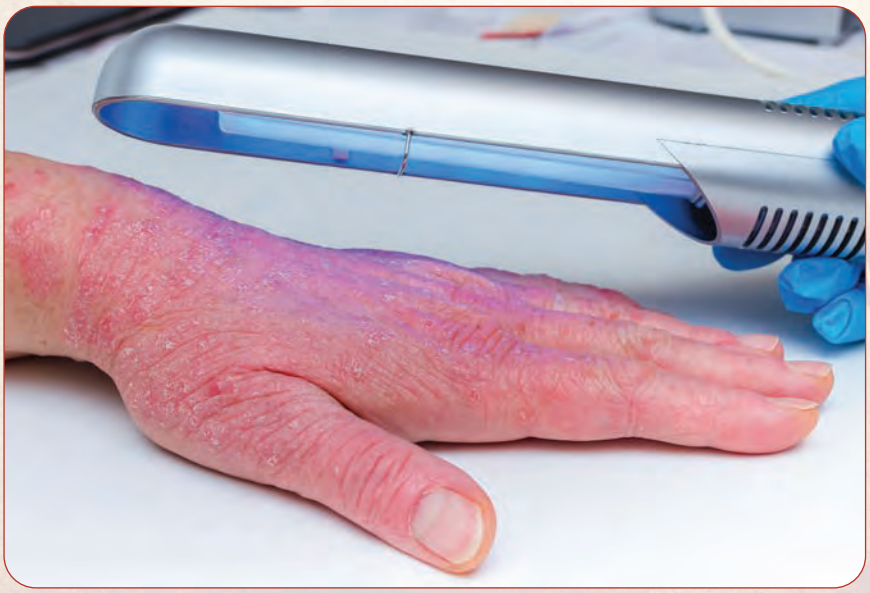
1970s – methotrexate and PUVA

Methotrexate, formerly known as aminopterin, was originally introduced in 1946 as a treatment for leukaemia. Some five years later it was found that aminopterin used in the treatment of rheumatoid arthritis also cleared psoriasis. In 1958, the more stable derivative of aminopterin with lower toxicity – methotrexate – was introduced. In 1972 the drug was approved for use in psoriasis.

Methotrexate works by suppressing the overactive immune system that causes psoriasis. It is a powerful medicine and nowadays is used to treat severe psoriasis and psoriatic arthritis. In most cases, psoriasis is cleared in four to six weeks. Unfortunately, it has several unwanted effects, most notably nausea, headaches and fatigue. It may also cause serious liver damage with long-term use. It is used in the treatment of cancer and various autoimmune diseases, including psoriasis. Methotrexate can be given as tablets, oral solution or by injection.

Another development of the 1970s was PUVA (psoralen and ultraviolet A) therapy, in which the patient is first given a psoralen (a drug containing chemicals that react with ultraviolet light) and then exposed to UVA light. Remarkably, it seems that this idea was known to the ancient Egyptians of around 1500 BC, who used a combination of sunlight and ingestion of plants known as psoralens – including limes and figs – to treat vitiligo (a loss of skin pigmentation).

In 1974 and 1977, the first trials of PUVA in the treatment of psoriasis showed that patients experienced clearing of their skin lesions. Nowadays it is used in the treatment of moderate to severe plaque psoriasis that has failed to respond to topical treatments. Although often therapeutically successful, PUVA therapy increases the risk of skin cancer and may also cause skin damage and premature ageing (all of which also occur with natural sunlight). For this reason, there are specific guidelines as to the total number of UV treatments an individual can have in a lifetime.



1990s – ciclosporin (or cyclosporine)

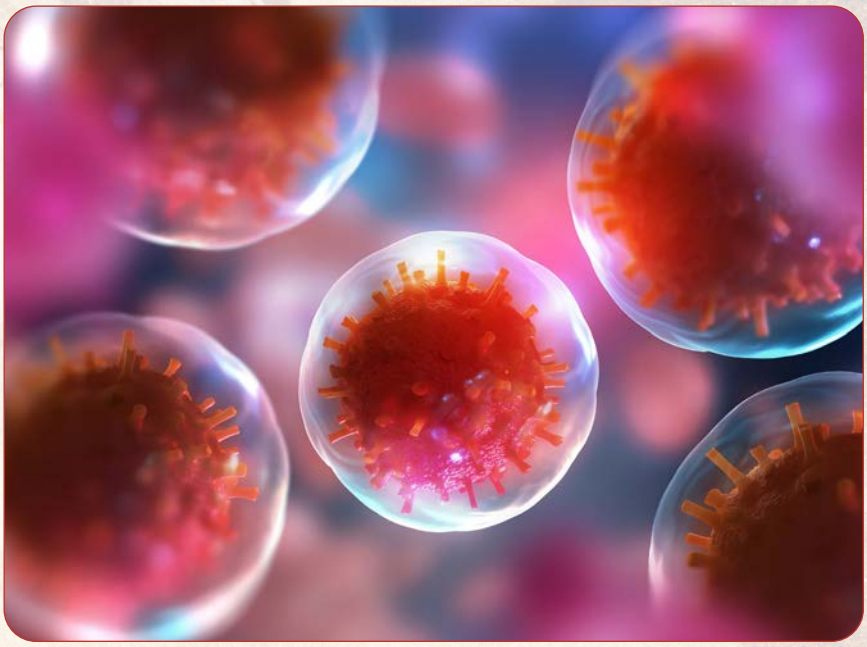
Ciclosporin (Neoral®, Sandimmun®) is a powerful immunosuppressive drug that was first used to help prevent rejection in organ transplant patients. In 1997, the US Food and Drug Administration (FDA) approved the use of ciclosporin for adults with severe psoriasis and otherwise normal immune systems. Ciclosporin suppresses the immune system and slows down the growth of certain immune cells. It is most often used in refractory psoriasis which has failed to respond to other systemic treatments.

Ciclosporin is thus another powerful weapon in the expanding armoury of treatments for psoriasis. As with other powerful medications, there are potentially serious unwanted effects, including high blood pressure, kidney damage and an increased susceptibility to infections.

The 1990s also saw the introduction of another important class of drugs, the Vitamin D analogues, which are for topical (applied to the skin) use and come in ointment, cream, gel and lotion applications. Note that these are not the same as the oral vitamin D supplements that you might take. Topical vitamin D treatments work by slowing down the over-production of skin cells (epidermal hyperplasia) which is the hallmark of psoriasis, and encouraging normal skin growth. They also have an anti-inflammatory effect.

There are four vitamin D treatments available in the UK – calcipotriol (Dovonex®}, calcitriol (Silkis®), tacalcitol (Curatoderm®) and a calcipotriol/steroid combination (Dovobet®).

2000-present – the advent of novel biologics



By far the most exciting development in the management of psoriasis has been the advent of biologics. The first two biologic agents - for the treatment of moderate-to-severe chronic plaque psoriasis - were approved by the FDA in 2003. There are currently around a dozen of these agents – including adalimumab (Humira®), etanercept (Enbrel®), ustekinumab (Stelara®), and secukinumab (Cosentyx®). The UK's National Institute for Health and Care Excellence (NICE) has recommended that these drugs can be prescribed for people with severe psoriasis who have not responded to other systemic treatments such as methotrexate, ciclosporin and PUVA. Biologics must be given by injection (or infusion) - they cannot be taken by mouth.

The latest class of biologics, known as Janus kinase (JAK) inhibitors – e.g. tofacitinib (Xeljanz®) – have a unique mode of action, in that they interrupt signalling between the cytokines responsible for the inflammatory response in psoriasis. JAK inhibitors may be especially beneficial in the management of psoriatic arthritis.

Biological therapies cannot be made simply by mixing various ingredients in a laboratory, the way conventional drugs are made. Instead, biologic therapies are made using living organisms, such as bacteria, yeast, and even mammalian tissue and cells. Insulin is a good example of a biologic treatment used in diabetes.

In addition, the mode of action of biologics is quite different from traditional systemic drugs that impact (and suppress) the entire immune system. Instead, biologics only target specific parts of the immune system. The biologics used to treat psoriatic disease block the action of a specific type of immune cell called a T-cell, or they block inflammatory proteins (cytokines) such as tumour necrosis factor-alpha (TNF-alpha), and interleukins (17A, 12 and 23). These cells and proteins all play an essential role in the development of the skin and joint manifestations of psoriasis.

Not all the latest drugs for psoriasis are classified as biologics. In 2016, apremilast (Otezla™) was approved for use in the UK. It is a systemic (oral) medication that can be used to treat moderate to severe psoriasis and psoriatic arthritis. Its precise mode of action is not entirely clear, but it is known to block an enzyme known as phosphodiesterase 4 (PDE 4), which is involved in the inflammatory response within the cell. Reducing the intensity of the inflammatory response in this way can help to improve symptoms in those with psoriasis and psoriatic arthritis.

Conclusion

Progress in science is always uneven, but our understanding of psoriasis as primarily an inflammatory condition has evolved at astonishing speed over the past few decades. Historically, treatments were often stumbled upon by chance and, in practice, were very blunt instruments which had potentially serious side-effects.

Today, a much more secure scientific foundation has opened the door to a new generation of targeted therapies – aimed at specific molecules in the inflammatory cascade. Consequently, our ability to treat patients and improve their quality of life has never been better. The history of psoriasis is, at the same time, the history of scientific progress.

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